I. AMENDMENT

Amendments to the Specification

- Please replace the title of the application shown on page 1, lines 2-4, with the following rewritten title:

-- ~~IDENTIFICATION OF UNIQUE BINDING INTERACTIONS BETWEEN CERTAIN ANTIBODIES AND THE HUMAN B7.1 AND B7.2 CO-STIMULATORY ANTIGENS~~
TREATMENT OF B CELL LYMPHOMA USING ANTI-CD80 ANTIBODIES THAT DO NOT INHIBIT THE BINDING OF CD80 TO CTLA-4 --

- Please replace the paragraph beginning at page 1, line 6, with the following rewritten paragraph:

-- This ~~application~~ is a continuation of U.S. Patent Application No. 08/746,361, filed November 8, 1996, now abandoned, which is a continuation-in-part of U.S. ~~application~~ Patent Application ~~Serial~~ No. 08/487,550, filed June 7, 1995, now U.S. Patent No. 6,113,898, issued on September 5, 2000. --

- Please replace the six consecutive paragraphs beginning at page 23, line 25, with the following six rewritten paragraphs:

-- Figure 3a depicts the amino acid and nucleic acid sequence of a primatized® form of the light chain of 7C10 (SEQ ID NO:1).

Figures 3b and 3c depicts the amino acid and nucleic acid sequence of a primatized® form of the heavy chain of 7C10 (SEQ ID NO:2).

Figure 4a depicts the amino acid and nucleic acid sequence of a primatized® form of the light chain of 7B6 (SEQ ID NO:3).

Figures 4b and 4c depicts the amino acid and nucleic acid sequence of a primatized® form of the heavy chain of 7B6 (SEQ ID NO:4).

Figure 5a depicts the amino acid and nucleic acid sequence of a primatized® light chain 16C10 (SEQ ID NO:5).

Figures 5b and 5c depicts the amino acid and nucleic acid sequence of a primatized® heavy chain 16C10 (SEQ ID NO:6). –

• Please replace the paragraph beginning at page 28, line 7, with the following rewritten paragraph:

-- The present inventors elected to immunize macaques against human B7.1 antigen using recombinant soluble B7.1 antigen produced in CHO cells and purified by affinity chromatography using a L307.4 ~~sepharose~~ SEPHAROSE® affinity column. However, the particular source of human B7 antigen, human B7.1 antigen or human B7.2 antigen is not critical, provided that it is of sufficient purity to result in a specific antibody response to the particular administered B7 antigen and potentially to other B7 antigens. - -

• Please replace the paragraph beginning at page 29, line 11, with the following rewritten paragraph:

-- After immunization B cells are collected, e.g., by lymph node biopsies taken from the immunized animals and B lymphocytes fused with KH6/B5 (mouse x human) heteromyeloma cells using polyethylene glycol. Methods for preparation of such heteromyelomas are known and may be found in U.S. ~~Serial No. 379,072 by Newman et al., filed on January 25, 1995 and~~ Patent No. 5,658,570, incorporated by reference herein. - -

• Please replace the paragraph beginning at page 30, line 4, with the following rewritten paragraph:

– Also, affinity purified antibodies from macaques were tested for their reactivity against CHO transfectants which expressed B7.1/Ig fusion proteins, and against CHO cells which

produced human B7.2 antigen. These results indicated that the B7.1 immune sera bound to the B7.2 transfectomas. Binding of antibodies to B7.2 antigen may be confirmed using soluble B7.2-Ig reagents. As discussed in the examples, this may be effected by producing and purifying B7.2-Ig from CHO transfectomas in sufficient quantities to prepare a B7.2-Ig ~~sepharose~~ SEPHAROSE® affinity column. Those antibodies which cross-react with B7.2 will bind the B7.2-Ig ~~sepharose~~ SEPHAROSE® column. - -

- Please replace the paragraph beginning at page 30, line 17, with the following rewritten paragraph:

- - Cell lines which express antibodies which specifically bind to human B7 antigen, B7.1 (CD80) antigen and/or B7.2 (CD86) antigen are then used to clone variable domain sequences for the manufacture of primatized antibodies essentially as described in Newman et al (1992), *Id.* and ~~Newman et al, U.S. Serial No. 379,072, filed January 25, 1995~~ U. S. Patent No. 5,658,570, both of which are incorporated by reference herein. Essentially, this entails extraction of RNA therefrom, conversion to cDNA, and amplification thereof by PCR using Ig specific primers. Suitable primers are described in Newman et al, 1992, *Id.* and in U.S. ~~Serial No. 379,072~~ Patent No. 5,658,570. (*See*, in particular, Figure 1 of U.S. ~~Serial No. 379,072~~ Patent No. 5,658,570). - -

- Please replace the paragraph beginning at page 31, line 14, with the following rewritten paragraph:

- - For example, this expression system has been previously disclosed to result in primatized antibodies having high avidity ($Kd \leq 10^{-10}$ M) against CD4 and other human cell surface receptors. Moreover, the antibodies have been found to exhibit the same affinity, specificity and functional activity as the original monkey antibody. This vector system is substantially disclosed in commonly assigned U.S. ~~Serial No. 379,072~~ Patent No. 5,658,570, incorporated by reference herein, as well as U.S. Serial No. 08/149,099, filed on November 3, 1993, now U.S. Patent No. 5,736,137, also incorporated by reference in its entirety herein. This system provides for high expression levels, i.e., > 30 pg/cell/day. - -

• Please replace the paragraph beginning at page 33, line 15, with the following rewritten paragraph:

-- Using the techniques described *supra*, and in commonly assigned U.S. ~~Serial No. 08/379,072~~ Patent No. 5,658,570, the present inventors have cloned the variable domains of 7C10, 7B6 and 16C10, and provide the amino acid and nucleic acid sequences of primatized forms of the 7C10 light chain, 7C10 heavy chain, 7B6 light chain, 7B6 heavy chain, 16C10 light chain and 16C10 heavy chain. These amino acid and nucleic acid sequences may be found in Figures 3a (SEQ ID NO:1), ~~and~~ 3b-3c (SEQ ID NO:2), 4a (SEQ ID NO:3), ~~and~~ 4b-4c (SEQ ID NO:4), and 5a (SEQ ID NO:5) and 5b-5c (SEQ ID NO:6), respectively. The DNA and amino acid sequence for the human gamma 1 and gamma 4 constant domains may be found in ~~08/379,072~~ U.S. Patent No. 5,658,570. --

• Please replace the paragraph beginning at page 33, line 26, with the following rewritten paragraph:

-- As discussed *supra*, these primatized antibodies are preferably expressed using the NEOSPLA expression vector shown in Figure 2 which is substantially described in commonly assigned ~~08/379,072~~ U.S. Patent No. 5,658,570 and ~~08/149,099~~ U.S. Patent No. 5,736,137, both of which ~~applications~~ are incorporated by reference herein. --

• Please replace the paragraph beginning at page 57, line 20, with the following rewritten paragraph:

-- Using the primatized antibody methodology incorporated by reference to commonly assigned U.S. ~~Serial No. 08/379,072~~ Patent No. 5,658,570, and using the NEOSPLA vector system shown in Figure 2, the heavy and light variable domains of 7C10, 7B6 and 16C10 were cloned and primatized forms thereof have been synthesized in CHO cells using the NEOSPLA vector system. The amino acid and nucleic acid sequences for the primatized 7C10 light and heavy chain, 7B6 light and heavy chain, and 16C10 light and heavy chain are respectively shown in Figures 3a (SEQ ID NO:1), 3b-3c (SEQ ID NO:2), 4a (SEQ ID NO:3), 4b-4c (SEQ ID NO:4), 5a (SEQ ID NO:5) and 5b-5c (SEQ ID NO:6). --

- Please add the following new captioned paragraph after line 10 on page 61:

Deposit Information

Hybridoma 7C10 and hybridoma 16C10, which produce antibodies 7C10 and 16C10, respectively, were deposited on May 29, 1996, with the American Type Culture Collection (ATCC), currently located at 10801 University Boulevard, Manassas, VA 20110-2209, under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure ("Budapest Treaty"). The ATCC has assigned hybridoma 7C10 the ATTC Accession No. HB-12117, and has assigned hybridoma 16C10 the ATTC Accession No. HB-12119.

- Please replace the abstract on page 66, with the following rewritten abstract:

– The present invention relates to the identification of antibodies which are specific to human ~~B7.1~~ CD80 antigen (~~CD80~~ B7.1) and which are capable of inhibiting the binding of ~~B7.1~~ CD80 to a CD28 receptor and which are not capable of inhibiting the binding of ~~B7.1~~ CD80 to ~~a~~ CTLA-4, a T cell receptor that down-regulates T cell responses. Two of these antibodies, 16C10 and 7C10, significantly inhibit the production of IL-2, in spite of the existence of a second activating ligand ~~B7.2~~ CD86 (~~CD86~~ B7.2). Blocking of the primary activation signal between CD28 and ~~B7.1~~ CD80 (~~CD80~~ B7.1) with these antibodies while allowing the unimpaired or coincident interaction of CTLA-4 and ~~B7.1~~ CD80and/or ~~B7.2~~ CD86 represents a combined antagonistic effect on positive co-stimulation with an agonistic effect on negative signalling. These antibodies, or CD80-binding fragments thereof, may be used ~~as specific immunosuppressants, e.g.,~~ for the treatment of ~~autoimmune diseases and to prevent organ transplant rejection~~ B cell lymphoma. --